Clinical Dimensions of Fatigue

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Because the symptom of fatigue is often vague, clinical evaluation requires the consideration of distinct features such as timing, precipitants, presence of libido, sleep quality, exercise capacity, and sedation. Fatigue has dimensions of affect and tolerability. In chronic illness, it is helpful to consider mood, physical conditioning, course of predictable treatment consequences, postural hypotension, and the well-being of caretakers. The differential diagnosis of acute and chronic fatigue is considered. Chronic fatigue of unknown etiology is placed in historical context, and an approach to the complexities of providing continuing evaluation and care is discussed.

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To evaluate fatigue, like pain, as a medical complaint requires attention to dimensions of sensation and affect. Patients come to the doctor with complaints about fatigue when they believe that there has been a change from the usual. As with other symptoms in medicine, taking a history means first understanding the complaint from the worldview of the patient. The first 5 minutes of the patient's description of the complaint gives data for many hypotheses. How did he or she come to recognize it? Why did he or she come to the doctor now? What precipitates fatigue, what perpetuates it, and what relieves it? What are the parameters that describe the symptom? How much effort does it take to get going? What is the quality of sleep? We know that disordered sleep can alter energy. Does sleep relieve fatigue? Is fatigue notable as the patient climbs stairs? Does the fatigue refer to the feeling of sleepiness or sedation during the day? How much exercise can the patient sustain, and what happens after exercise? Is there a time of day when fatigue is worse?

CLINICAL DIMENSIONS OF FATIGUE

Emotional Aspects

Fatigue has an emotional dimension. A patient who is anxious may be more tired due to the stress of chronic anxiety. After a panic attack, patients feel exhausted. Anticipatory anxiety and the tendency to avoid a stressful encounter may be explained in words that sound like a complaint of fatigue, for instance, "I am too tired to go to the party." The fear of embarrassment, fear of going outside (agoraphobia), or fear of going back to locations of previous panic attacks can appear to be related to lack of energy rather than to avoidance. When the patient has a conflict about whether to go forward, the inability to make a decision or the ambivalence about what to do may be described as fatigue.

Major depressive disorder itself, as well as grief, loss, and sadness, is associated with feelings of fatigue. To chronically suppress anger takes effort and also tires. Depressive disorder includes anhedonia, the inability to sense pleasure. The opportunity for pleasurable activities to add energy is eliminated. When there is no libido or interest, there is no inclination to initiate action. Dread fills the morning, and the patient tends to delay getting out of bed. Movement is effortful. Insomnia or the tendency to sleep too much comes with the syndrome and leads to another layer of fatigue related to sleep deprivation. Some patients with atypical depression have a feeling of leaden legs or walking through molasses; this is a somatic description of the effortful nature of the fatigue of depression.

The absence of desire raises the question not only of depression, but of apathy. Apathy is the lack of initiative even without dysphoria. The differential diagnosis of apathy includes dementia, particularly frontal lobe dysfunction, and endocrine deficiency like hypothyroidism, hypopituitarism, and prolactinoma. A patient may also inhibit desire because of anticipated anxiety, when avoidance is the more natural option.

Finally, as in McGill's pain questionnaire,[1] there is a bearable or unbearable quality to the symptom of fatigue. The ability to bear the symptom captures the elements of humiliation, helplessness, and hopelessness that persistent fatigue arouses. Does the patient feel worthless, and is he or she unable to care for himself or herself, vulnerable to sadistic behavior, or easily demeaned? Is the patient impotent?

Sleep

Clinical assessment of fatigue requires an evaluation of sleep. A detailed sleep history becomes laboratory data. Is the patient napping in the day long enough to interfere with night sleep? Does pain interfere with sleep? Does snoring suggest sleep apnea, leg movements suggest rest-

less legs syndrome, or paroxysmal nocturnal dyspnea suggest congestive heart failure? The paradigm of physical causes of fatigue is sickness behavior—the malaise, listlessness, inability to concentrate, hypersomnia, anorexia, constricted social activities, loss of interest, and poor grooming that occur in an animal who is ill.[2] This behavior is associated with systemic disease and elevated cytokines. Cytokines increase slow-wave sleep, which may explain the hypersomnia of malaise.[3]

Differential Diagnosis

Organic causes of fatigue include active cancer, infection, diabetes, hypercalcemia, anemia, rheumatic disease, neurologic injury, and adrenal, thyroid, hepatic, or renal insufficiency. Cardiopulmonary disease makes exertion more difficult, and myopathy limits movement. Medications and substance abuse, particularly sedating medications, add another field of analysis. Physical examination should focus on vital signs, lymphadenopathy, and abnormalities of the thyroid, heart, lung, and central nervous system.

Laboratory Tests

Many years of research into the causes of chronic fatigue syndrome have established a finite number of laboratory tests that are usually adequate to rule out medical causes of fatigue in a patient with normal physical examination results and no focused complaints.[4] These tests include the complete blood count, blood urea nitrogen, creatinine, electrolytes, calcium, phosphate, total protein, creatine kinase, liver function, sedimentation rate, antinuclear antibody, rheumatoid factor, and thyroid-stimulating hormone. Corroboration of cancer screening tests such as cervical smear and mammogram may be helpful.

Serology for syphilis, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, toxoplasmosis, and Lyme disease must be understood within the clinical context. Acute mononucleosis is associated with fever, lymphadenopathy, pharyngitis, and elevation of Epstein-Barr virus titers, but chronic reactivation of the virus does not explain chronic fatigue.[5] Similarly, evidence of Lyme disease with no other signs of illness may only indicate that the patient has had Lyme disease in the past and not relate to present symptoms.[6] Studies of brain function like magnetic resonance scans, lumbar puncture, and electroencephalogram may broaden the considerations if multiple sclerosis or seizures are in the differential diagnosis. Similarly, the necessity of scans to search for occult malignancy depends on clinical context.

Fatigue in Major Illnesses Such As Cancer

Cancer patients who do not have recurrent disease can experience different patterns of fatigue from chemotherapy, radiation treatment, or surgery.[7] Strategies for treatment include rest, systematic physical therapy, and stimulants. It is helpful for the patient to know that some fatigue is a normal consequence of treatment independent of mood. Their fatigue is likely to get substantially better and does not by itself indicate recurrent tumor.

One cause of weakness in this setting of cancer treatment is postural hypotension, a measurable vital sign that can be followed clinically. It is a consequence of some anticancer agents (like cisplatin and etoposide), anemia, and autonomic neuropathy. These may together make a patient weak on standing or sitting and limit his or her capacity for exertion. Sometimes, antihypertensive medications have not been reduced when the patient becomes ill, so the appropriate intervention is proper adjustment of the antihypertensive regimen. Bed rest and physical deconditioning contribute another element to postural hypotension, weakness, and fatigue.

For the patient with cancer, principles that reduce fatigue include the recommendation to reduce analgesics and other medications in order to treat pain but minimize sedation. Patients should make time for sleep at predictable hours in a comfortable environment. To guarantee enough energy in the social system, patients must allow caregivers flexibility, so that they do not burn out. Caretakers, in their fashion, lend their energy. Patients are advised to conserve energy as if in an energy budget, to set priorities, to delegate what can be delegated, and to consider what brings pleasure and therefore adds energy.

CHRONIC FATIGUE SYNDROME

When patients come to the doctor's office with a question relating to chronic fatigue or chronic fatigue syndrome, their symptom must be placed in a normal context. About one quarter of adults are fatigued for 2 weeks or more, and about 60% of these cases have no identified medical cause.[8,9] About one quarter of primary care patients have prolonged fatigue of 1 month or more.[10] The definition of chronic fatigue syndrome requires more than 6 months of fatigue. The formal chronic fatigue syndrome adds dimensions of impaired memory or concentration, sore throat, tender cervical axillary lymph nodes, muscle pain, multi-joint pain, new headaches, and unrefreshing sleep or postexertional malaise.[4] The prevalence of patients who meet the definition of chronic fatigue syndrome is small: 75 to 267 per 100,000.[11] Idiopathic chronic fatigue occurred at a rate of 2300 to 6300 per 100,000 individuals in a survey of members of a health maintenance organization.[12] In the medical population, the patients who present with this syndrome are more often women.[13]

Finding one etiology and one treatment for chronic fatigue syndrome has never been simple. Infectious, immunologic, and hormonal abnormalities have been sought. Abnormalities in the hypothalamic-pituitary-adrenal axis and in the brain have been noted in some populations.[14]

Autonomic nervous system dysfunction has been noted in others. The description of chronic fatigue syndrome has been seen as part of the spectrum of mood or attentional disorders. Sleep disorder is also a consideration.

The population of chronic fatigue syndrome patients is heterogeneous, and the prognosis has varied widely. On the one hand, gradual improvement is noted over 6 months. On the other, 12% of patients have been noted to remit, and half of those to later relapse.[15] Variables that mark poor outcome include medical disability or retirement,[16] long duration of illness, lifetime dysthymia,[17] conviction of chronic fatigue syndrome (the unshakable belief that this is the diagnosis), untreated psychological distress, and avoidant coping strategies.[18,19] The patient's premorbid personality colors the presentation of the syndrome; the premorbid features have been described as hard-driving, perfectionist, obsessive-compulsive, and overactive.[20,21] Loneliness can be an unmeasured variable.

History of Chronic Fatigue Syndrome

Neurasthenia, a diagnosis characterized by chronic fatigue, was defined by George Beard in the best-selling book *American Nervousness*.[22] The term *neurasthenia*, first used in 1869, meant "lack of nerve force" and was thought to be related to actual loss of nerve strength. Associated symptoms were headaches, loss of hearing, near-sightedness, increased blushing, bad dreams, dyspepsia, excessive sweating, tremulousness, general weakness, scalp tenderness, cramps, heart palpitations, phobias, increased ticklishness, flying neuralgias, chills, cold feet, cold hands, tooth decay, excessive yawning, impotence, and vaginismus.[22] S. Weir Mitchell, the father of neurology, subsequently systematized the "rest cure," a program of good nutrition, respites at spas, and massages.[23] By the 1900s, brain fatigue was seen as emotional rather than literal nerve fatigue.[24] Anxiety neurosis and depression, or psychasthenia, were concepts that distinguished some patients who would have fallen under the rubric of neurasthenia. Janet, who defined psychasthenia and asthenia, advised patients on how to use their energy budget.[25] Research on fatigue in the early 20th century led to further understanding of neurocirculatory asthenia, or anxiety disorder. "Operational fatigue" was a World War II euphemism for all nervous reactions to combat. Menninger described neurotic fatigue as a deficit resulting from misdirected energy rather than lack of energy.[26]

Medical Assessment of Chronic Fatigue

The relationship between physician and patient and careful attention to the history are key to understanding chronic fatigue syndrome in a particular patient.[27] The traditional acquisition of the patient's story at the onset of fatigue becomes a window into the diagnostic mystery. History taking in the medical interview allows the opportunity for the physician to hear the patient's story and to offer the patient respect. In the interview, the physician hears how the patient feels about the predicament. The physician's empathy and understanding deepen the relationship between doctor and patient and become, in themselves, part of the treatment. Past medical history and history of depressive or other psychiatric disorders add to the analysis. A history of medically unexplained symptoms and repeated medical evaluation raises the question of somatoform disorders and increases the chance that past medical records will shed light on the diagnosis. Documentation of substance abuse and prescription or over-the-counter medications allows consideration of these common exacerbating factors.

Comprehensive history taking includes gathering information on fatigue, other somatic symptoms, sleep description, cognitive difficulties, disability, and distress. The patient explains his or her own beliefs about health and disease, treatment history, and coping strategies of physical rest or avoidance of stress. The role that family members, finances, and employment play in the patient's choices should be explored. The patient's lifestyle and premorbid personality define context. It would not be surprising to find that previous medical assessments have not been so comprehensive and that few physicians have taken the time to know the patient.

Mental status examination assesses mood, cognitive function, memory, and personality. Depression, anxiety, self-destructive thoughts, delusions, and physical signs of psychomotor retardation are noted. The basic laboratory tests noted above are adequate to rule out obvious medical causes. Further testing is determined by specific aspects of the history or physical examination. Neuropsychiatric testing may amplify the data from the mental status examination. The psychiatric differential diagnosis includes depression, dysthymia, anxiety disorders, attention deficit disorder, somatoform disorder, eating disorder, dementia, schizophrenia, bipolar disorder, drug or alcohol abuse, and specific neuropsychiatric deficits. Neuropsychiatric deficits in executive function, language-learning difficulties, and attentional difficulties may highlight why the patient is less able to initiate function, pay attention, or solve problems. The data may give clues to a specific cause of neurologic injury or merely document chronic disabilities that lead to increased frustration.

Treatment of Chronic Fatigue

The treatment strategy begins with a comprehensive review of the findings, good sleep hygiene or clarification of sleep disorders, patterns of eating, and treatment of diagnosed psychiatric illness. Cognitive rehabilitation may have a role for those with documented neuropsychiatric deficit. The physician must be attentive to transference and countertransference in the assessment and treatment plan. Graded physical exercise (manageable portions throughout the day) and cognitive-behavioral treatment

are the major tools for further treatment. Reduction of daytime naps, stable rising time, and time out of bed become features that can be modified. Diaries are an important method of recording the contributions to fatigue in the real world.

Key elements of cognitive-behavioral treatment are goal setting, education about the illness, relaxation training, exposure to avoided activities, and restructuring of potential misinterpretations.[27] Distressing negative thoughts, such as fear about symptoms, drive to perfectionism, sensitivity to criticism, and guilt about failure, can be targeted. Together, the patient and physician also look at what elements of the patient, family, or social structure perpetuate and reinforce the disability. The challenge of coping with setbacks becomes key to the continuing treatment.

No one somatic treatment for chronic fatigue syndrome has been identified. The comprehensive program requires optimal psychopharmacologic treatment of psychiatric diagnoses that may contribute to fatigue. Medical evaluation at regular intervals can assess the patient to be sure that all new symptoms are not attributed to a chronic diagnosis, but medical testing need not be overdone if the physician has an ongoing relationship with the patient and can recognize changes. The principles of cognitive-behavioral treatment become keys to improving patient function and quality of life, but these changes may not be sustained.[28,29] The problem of relapse must be managed by the physician in an even-handed, nonjudgmental way just as he or she should cope with relapse in addiction. Improvement in chronic fatigue syndrome will often require complex behavioral change despite the tendency for fatigue to overwhelm and limit productivity.

Drug names: cisplatin (Platinol and others), etoposide (Vepesid, Toposar, and others).

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